51. (Previously presented) The culture of claim 1 or 3 wherein greater than 50% of differentiated neuronal cells are immunoreactive with striatal neuronal markers.

52. (Previously presented) The culture of claim 51 wherein said striatal neuronal markers are DLX1 and/or MEIS2.

53. (Previously presented) The culture of claim 1 or 3 wherein greater than 50% of differentiated neuronal cells are immunoreactive with cortical neuronal markers.

54. (Previously presented) The culture of claim 53 wherein the cortical neuronal markers is PAX3.

55. (Previously presented) The culture of claim 1 or 3 wherein greater than 50% of differentiated neuronal cells are not immunoreactive with neuronal markers of the medial ganglion eminence.

56. (Previously presented) The culture of claim 55 wherein one of said neuronal markers of the medial ganglionic eminence is NKX2.1.

REMARKS

Claims 1-15, 17-23 and 42-56 are currently pending in this application. Applicants acknowledge with appreciation the Examiner's withdrawal of various objections and rejections as detailed in the May 13 Office Action.

Applicants have amended the specification to refer to Figure 5 as comprising parts "A" and "B".

Claims 1, 3, and 22 have been amended to recite "wherein the proliferation inducing growth factor is selected from the group consisting of EGF, amphiregulin, acidic fibroblast growth factor, basic fibroblast growth factor, transforming growth factor alpha, and combinations thereof." Support for this amendment can be found in the specification, for example, on page 12, lines 11-13.

Claim 42 is amended to recite that the cells are "non-tumorigenic". Support for this amendment can be found in the specification, for example, on page 16, line 6-7. On page 16, the cells are referred to as NS4 cells. NS4 cells express GFAP and nestin as described on page 6, lines 16-20.

Claim 16 has been canceled.

None of the amendments presented herein constitute new matter. Applicants reserve the right to pursue canceled subject matter in applications claiming priority to the instant application. Applicants address below the outstanding objections and rejections.

THE INFORMATION DISCLOSURE STATEMENT

The Examiner has objected to the previously filed Information Disclosure Statement contending that it failed to comply with 37 C.F.R. 1.98(a)(2). Applicants have filed herewith the requested documents.

THE OATH/DECLARATION

The Examiner objected to the oath/declaration contending that it was not signed by Kenneth Campbell. Applicants believe the previously filed oath/declaration was signed by Kenneth Campbell, however, applicants are enclosing herewith another copy of that document.

THE DRAWINGS

The Examiner has objected to the drawings, contending that the specification does not describe Figure 5 as comprising parts "A" and "B". Applicants have amended the specification herein to correctly refer to the amended drawing.

CLAIM OBJECTIONS

The Examiner has objected to claim 16, contending that the word "inhibitor" is misspelled. Applicants have canceled claim 16 herein.

Accordingly, applicants request that the outstanding objection be withdrawn.

THE REJECTIONS

35 U.S.C. § 112, first paragraph

Claims 1-21 and 50-56 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that the specification does not reasonably provide enablement for proliferation-inducing growth factors other than EGF. Office Action, page 4-5. The Examiner has further rejected claims 22, 23 and 43-49 under 35 U.S.C. § 112, first paragraph and has cited a number of patents and publications in support of the rejection. Applicants traverse.

The Examiner asserts that the use of growth factors is unpredictable and requires extensive experimentation. While applicants maintain that the claims as filed are enabled, in order to expedite allowance of the pending claims, applicants have amended claims 1, 3 and 22 (and, therefore, those claims dependent therefrom) to recite EGF and several closely related growth factors that demonstrate predictable biological activity based on the data presented in the present application and in view of the knowledge of the skilled person. The use of these growth factors is described in the specification, in particular on page 12-13. Applicants believe this amendment is consistent with the Examiner's statement that the specification is enabling for the use of EGF and respectfully request that the Examiner consider the following remarks.

The present application presents data on the use of EGF and a combination of EGF and bFGF for induction of cell proliferation. Amphiregulin and TGF-alpha are capable of binding to and activating the EGF receptor and their use is therefore predictable in view of the data on EGF

(See e.g. David et al 1996). Acidic FGF signals through all the receptors that basic FGF can signal through and the use of acidic FGF is therefore as predictable as is the use of basic FGF.

The art also teaches that these five growth factors can be used for induction of proliferation in various CNS derived cells. Santa-Olla and Covarrubias (1995), cited by the Examiner, documents that the effect of EGF, bFGF and TGF-alpha and combinations of these is equivalent in terms of induction of cell division in complex cell compositions from the CNS. The data provided in the reference clearly show that similar results are obtained with these three mitogens and with combinations of them (see in particular the abstract and figures 2 and 3). In that respect, the Examiner has cited US 2003/0032181 which teaches that the use of EGF, FGF-2 (basic FGF) and TGF-alpha is equivalent in terms of production of glial cells from neural stem cells (see the abstract and Figure 1). US 6,404,180 (Johe) also mentions this group of growth factors as equivalent for proliferation of CNS stem cells (col 8, lines 20-21 and claim 1, step 4). This is also true for US 5,753,506 (Johe) (see column 11, lines 57-59). US 6,497,872 (Weiss et al) also discloses the group of growth regulators recited in the independent claims of the present application as the preferred growth regulators for proliferation of neural stem cells (column 16, line 67 to col 17, line 4).

The Examiner has cited Daadi and Weiss (1999), contending that the article teaches that growth factors vary in their effects on cells including astrocytes. The Examiner further contends that such cells are a type of $GFAP^+$ cell and, therefore, the article suggests an unpredictability exists with respect to the use of growth factors. Daadi and Wiess is concerned with the effect of various mitogens on induction of TH expression in neural cells taken from different regions of the CNS. The cells used in Daadi and Weiss are selected based on the position in the CNS. In contrast, the cells of the present invention are selected based on the expression of GFAP. Therefore, Daadi and Weiss cannot be used to show unpredictability for GFAP expressing cells from the CNS. In addition, Daadi and Weiss use conditioned medium in addition to bFGF. Conditioned medium is an ill-defined mixture of components and the results should therefore be interpreted with great care and do not allow generalization of the results, in particular not to other cell types. Therefore, any unpredictability noted in the article cannot be extended to the present invention.

The Examiner has cited Kalyani et al (1998), contending the reference teaches that neuronal restricted precursor cultures are "notoriously heterogenous and respond to a variety of extracellular signals." However, the cells of the present invention are distinguished from those used by Kalyani in that they are not only less heterogenous but, importantly, are selected based on the expression of GFAP. Even if the Examiner's conclusions are correct with respect to the teaching of Kalyani, there is no suggestion that Kalyani (or in the Examiner's citation of Kalyani) that $GFAP^+$ cells, as claimed in the instant invention, are "notoriously heterogenous and respond to a variety of extracellular signals." In fact, Kalyani makes no conclusions at all about such a class of cells. The Examiner further contends that Kalyani suggests the cellular response to a proliferation-inducing factor will vary depending on the homogeneity of the culture and the stage of development. The Examiner also asserts that Kalyani teaches that cloned cultures vary in their responsiveness to neurotransmitters. However, again, this is irrelevant to the present invention which relates to a culture of GFAP expressing cells in the presence of a mitogen. The Examiner goes on to contend that Kalyani teaches that reaction to a particular proliferation inducing factor varies depending on the homogeneity of the culture and the stage of development. Again, the present invention is restricted to a culture of a relatively homogenous group of cells of which at least 90% express GFAP. Kalyani failed to consider the responsiveness of such a group of cells. Even if it is true that Kalyani et al demonstrates that the effect of BMP-2 is dependent on age of the cultured cells and on which cells are present in the mixed population (i.e. page 8766), BMP-2 is not a mitogen but actually inhibits cell division and promotes cholinergic differentiation (see abstract of Kalyani et al). Accordingly, the teaching of Kalyani is not relevant to the instant invention.

Finally, the Examiner cites US 6,040,180 (Johe) as proof of unpredictability in the art. The Examiner contends that Johe "reviews several papers concerning the use of proliferation-inducing factors to stimulate cell differentiation in multipotent and stem cells derived from mammalian CNS". However, Johe is, at best, indicative of the state of the art at the time US 6,040,180 was filed (i.e. 1996). Johe may refer to different cells types, however, any observations regarding unpredictability in diverse cell preparations does not apply to the instant invention which utilizes a culture of a relatively homogenous group of cells of which at least

90% express GFAP.

Accordingly, applicants respectfully request that the Examiner consider the amended claims and withdraw the outstanding rejection.

35 U.S.C. § 102(b)

Claims 42 stands rejected under 35 U.S.C. § 102(b). Specifically, the Examiner contends that United States Patent No. 5,338,839 teaches "a tumor-derived cell line (U251 MG) which [is] immunopositive for GFAP and nestin thus meeting the limitations of claim 42." Applicants traverse.

Claim 42 has been expressly amended to recite a population of cells which is non-tumorigenic. In contrast, as the Examiner notes, the cell compositions of US 5,338,839 (see Table 1) are all tumor-derived cells. For this reason, the '839 patent cannot anticipate the claimed invention. One of skill in the art would understand the dangers of using tumor-derived cells for transplantation. Accordingly, applicants respectfully request that the Examiner withdraw the outstanding rejection.

CONCLUSION

Applicant respectfully requests that the Examiner enter the requested amendments, consider the foregoing remarks and withdraw the outstanding rejections. Should the Examiner feel that a telephone conference would expedite allowance of the pending claims, he is invited to call the undersigned.

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Respectfully submitted,

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